ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2015, **51**, 6528

Received 8th January 2015,
Accepted 6th March 2015

DOI: 10.1039/c5cc00181a

www.rsc.org/chemcomm

Ruthenium-catalyzed aerobic oxidative decarboxylation of amino acids: a green, zero-waste route to biobased nitriles†

Laurens Claes, Jasper Verduyckt, Ivo Stassen, Bert Lagrain and Dirk E. De Vos*

Oxidative decarboxylation of amino acids into nitriles was performed using molecular oxygen as terminal oxidant and a heterogeneous ruthenium hydroxide-based catalyst. A range of amino acids was oxidized in very good yield, using water as the solvent.

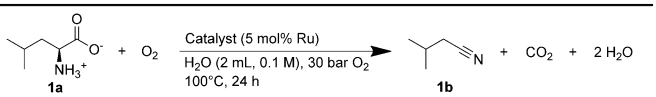
Nitrogen-based functionalities, in particular amines and amides, are present in a broad range of commodity and fine chemicals. They are often prepared by hydrogenation or hydration of nitriles, which are themselves the result of the metal-catalyzed incorporation of nitrogen into an organic backbone. Exemplary industrial processes are the ammoxidation of propylene into acrylonitrile or the hydrocyanation of butadiene into adiponitrile.[1] Nevertheless, the harsh process conditions or the need for toxic reagents (*e.g.* HCN) are strong incentives to explore milder production routes.

Proteins isolated from non-edible biomass, for instance the waste from agro-industry, biofuel production and slaughterhouses, provide an excellent renewable resource for producing N-containing chemicals.[2] Recently, we have shown that amino acids, obtained by hydrolytic protein depolymerization, can be recycled directly and with high selectivity into functionalized nitriles *via* bromonium-mediated oxidative decarboxylation.[3] In the conversion of glutamic acid and glutamine into biobased acrylonitrile,[4] adiponitrile[5] and succinonitrile,[6] this oxidative decarboxylation has been identified as a key step. However, product workup may be complex with halonium-type oxidants, *e.g. N*-bromosuccinimide.[7] Catalytic halide oxidation allows to reduce the waste load significantly,[3,8,9] but the reaction still suffers from limited yields based on hydrogen peroxide, and from an undesired oxidative ring halogenation of aromatic amino acids.[3]

Inspired by the transition metal-catalyzed oxidation of primary amines into nitriles using green oxidants,[10–13] we here present the first report on oxidative amino acid decarboxylation using molecular oxygen as the sole oxidant and a ruthenium-based catalyst, without involvement of halides or halonium species. Various nitriles were produced in water under mild conditions and, more importantly, in a fully salt-free process.

First, simple ruthenium compounds were evaluated on their activity in the oxidative decarboxylation of leucine, which serves as a model amino acid (Table 1). Reactions were performed in water, at 100 °C and initially under high oxygen pressure to avoid shortage of dissolved oxygen. With a homogeneous catalyst like $RuCl_3$, high conversions were obtained within 24 h. The reaction proceeds faster in neutral or basic media after adjusting the pH of the aqueous solution of $RuCl_3$. Irrespective of the pH, nitrile selectivity was affected by the consecutive hydration to the corresponding amide (entries 1–4).[14,15] Earlier studies on the related aerobic oxidation of primary benzylamines and

Table 1 Catalyst screening for aerobic oxidative decarboxylation of leucine



	Catalyst	X^a [%]	S^b [%]
1	—	<1	—
2	$RuCl_3$, pH 4	66	83
3	$RuCl_3$, pH 7	>99	78
4	$RuCl_3$, pH 10	>99	75
5	$Ru(acac)_3$[c]	94	88
6	γ-Al_2O_3	<1	—
7	$Ru(OH)_x/\gamma$-Al_2O_3	>99	78
8	Ru^{n+}/hydroxyapatite[d]	>99	76
9	$Ru(OH)_x$/hydroxyapatite	>99	80
10	$Ru(OH)_x/ZrO_2$	>99	69
11	$Ru(OH)_x$/hydrotalcite	>99	40
12	$Ru(OH)_x/TiO_2$	88	78
13	$Ru(OH)_x/CeO_2$	68	82
14	$Ru(OH)_x/Co_3O_4$	55	84
15	Ru^0/Al_2O_3[e]	46	85
16	Ru^0/C[e]	>99	14

[a] Leucine conversion. [b] Isovaleronitrile selectivity. [c] Acac: acetylacetonate. [d] Prepared by ion-exchange of Ca^{2+} with Ru^{3+}.[12a] [e] 5 wt% Ru^0 on support.

Centre for Surface Chemistry and Catalysis, Department of Microbial and Molecular Systems, KU Leuven – University of Leuven, Kasteelpark Arenberg 23, post box 2461, 3001 Heverlee, Belgium. E-mail: Dirk.DeVos@biw.kuleuven.be

† Electronic supplementary information (ESI) available: Experimental details, data on catalyst characterization (PXRD, SEM, EDX, N_2 physisorption) and additional results on oxidative decarboxylation. See DOI: 10.1039/c5cc00181a

aliphatic amines in water demonstrated that ruthenium catalyzes both amine oxidation and nitrile hydration;[14b] the latter reaction already occurs to a minor extent at 100 °C.[12e] Literature shows that one may increase the nitrile yield by working in nonpolar solvents like toluene[11a,12a] or trifluorotoluene,[12b] but such media are unsuitable to dissolve zwitterionic amino acids. While keeping water as the solvent, a significant improvement of the nitrile selectivity, even at high conversion, was achieved by using $Ru(acac)_3$ instead of $RuCl_3$ (entry 5).

Given the remarkable activity of ruthenium in amino acid oxidative decarboxylation, supported ruthenium catalysts were evaluated next, since they offer advantages in terms of product separation and metal recyclability. Typical catalysts were prepared according to the method of Mizuno and coworkers: ruthenium was immobilized onto a support by precipitation-deposition as hydrous ruthenium oxide in highly alkaline medium.[12] Candidate supports were commercially available oxides such as γ-Al_2O_3, ZrO_2, TiO_2 (anatase), CeO_2 and Co_3O_4, from which many successful catalysts have been developed for aerobic amine oxidation.[12b–i] Also hydroxyapatite[12a] and hydrotalcite were selected because slightly basic conditions seem to be beneficial for amino acid oxidation. Characterization by powder X-ray diffraction (PXRD) allowed to confirm that the structures of the supports were retained during alkaline deposition; *via* elemental analysis, the catalyst's actual ruthenium content was determined (Fig. S1–S10† and Tables S1 and S2†). It is well known that such a deposition procedure results in ionic Ru^{n+}, rather than metallic Ru^0 on the support.[12h,16]

High conversions of leucine were observed using ionic ruthenium supported on γ-Al_2O_3, ZrO_2, hydroxyapatite and hydrotalcite (Table 1, entries 7–11). The lower activity of the TiO_2-, CeO_2- and Co_3O_4-supported catalysts could be due to lower external surface areas, resulting in poor metal dispersion, but also the acid–base properties of the supports could play a role (entries 12–14, Table S3†). In addition to the catalysts based on ionic ruthenium, also metallic Ru^0 catalysts supported on Al_2O_3 and carbon were evaluated (entries 15 and 16). Although full conversion of leucine was obtained with Ru^0/C, nitrile selectivity was very low; the main reaction was an oxidation at the beta-carbon atom, leading to further skeleton breakdown and isobutyric acid formation. Clearly, the presence of ionic ruthenium is essential for selective oxidation. The most performant catalysts, *viz.* $Ru(OH)_x/\gamma$-Al_2O_3 and $Ru(OH)_x$/hydroxyapatite induce a weakly basic pH in the aqueous solution (Table S3†).

Upon variation of the reaction conditions it became clear that oxidative decarboxylation also proceeds smoothly at lower oxygen pressures, *e.g.* 5 bar (Fig. S11†). The reaction is first order in ruthenium (1–5 mol%, Fig. S12†) and by using a catalyst loading of 5 mol%, full leucine conversion is reached within an acceptable time frame (Fig. 1). The mild reaction temperature of 100 °C is close to the optimum: at slightly higher temperatures (*e.g.* 110 °C) a similar nitrile yield can be obtained within even shorter reaction times, whereas leucine conversion is significantly slower at 80 °C (Fig. S13†). When the reaction was performed at 150 °C for 24 h, isovaleramide was obtained as the major product (76% yield).

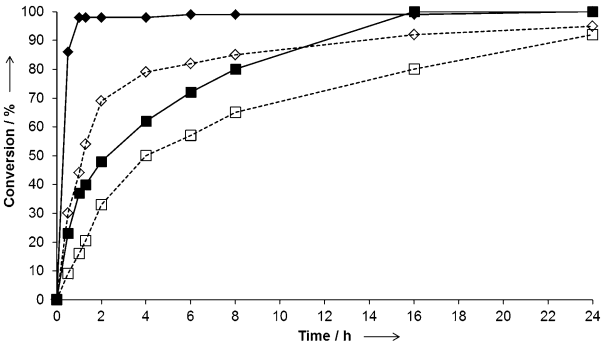


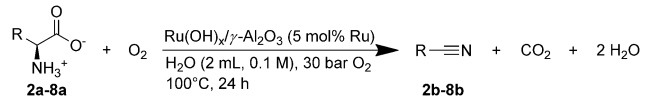
Fig. 1 Ru-catalyzed aerobic oxidation of *n*-pentylamine (◆) and leucine (■) as pure compounds (closed symbols) and in a 1 : 1-mixture (open symbols). Conditions: substrate (0.2 mmol), $Ru(OH)_x/\gamma$-Al_2O_3 (5 mol% Ru), H_2O (2 mL), O_2 (30 bar), 100 °C; the Ru-loading was 2.5 mol% in the competitive experiment.

The substrate scope of the $Ru(OH)_x/\gamma$-Al_2O_3 catalyst was successfully extended towards other amino acids bearing an aliphatic moiety, such as alanine (**2a**), valine (**3a**), isoleucine (**4a**) and norleucine (**5a**) (Table 2). These compounds behave similarly as leucine (**1a**): near-complete conversion is reached within 24 h, with a nitrile selectivity around 80%. Also glutamate (**6a**), which is the most abundant amino acid constituent from protein-rich waste streams derived from plant biomass,[2] was converted for 80% with high selectivity to the bifunctional nitrile **6b**. Interestingly, aspartate (**7a**) was much less reactive. On the one hand, this could be due to a chelating effect of the aspartate on surface Ru^{n+} species. On the other hand, the electron-withdrawing carboxylate group of the side chain is closer to the reactive α-carbon atom in aspartate than in glutamate; it is conceivable that the amino acid oxidation by Ru^{n+} is more sensitive to such electronic effects than the oxidative decarboxylation by strongly oxidizing halonium species.[3] A decreased reactivity was also observed for homoserine (**8a**), whereas serine and threonine showed little if any reaction. In addition, supported ruthenium catalysts facilitate aerobic alcohol oxidation as well,[17] resulting in complex product mixtures.

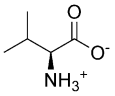
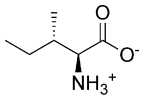
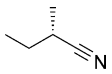
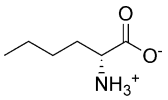
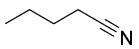
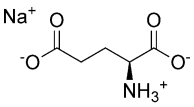
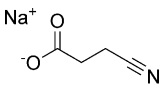
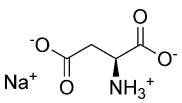
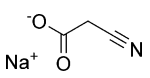
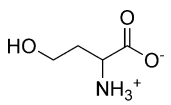
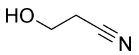
The heterogeneity of the $Ru(OH)_x/\gamma$-Al_2O_3 catalyst was demonstrated in the oxidative decarboxylation of **6a**. After 2 h, when the conversion was at 11%, the catalyst was separated and the filtrate did not show any residual activity (Fig. S14†). The catalyst was successfully recycled several times in the reaction of **1a**; while substantial activity remained in the re-use cycles, the reaction rates were lower (Table S4†). As for the oxidation of simple amines, it might be necessary to optimize the catalyst recycling procedures.

The oxidative decarboxylation of leucine proceeds much more slowly than the oxidation of *n*-pentylamine; the latter reaction remains preferred in competitive experiments (Fig. 1). However, in previous work from our group on alcohol racemization using supported ionic Ru^{n+}, it was found that the presence of carboxylates inhibited the dehydrogenation of alcohols on supported Ru^{n+}.[18] In this respect, the high activity of ruthenium catalysts for amino acid dehydrogenation is remarkable, especially in case of glutamate **6a**, which even contains an additional carboxylate group.

Table 2 Scope of the Ru-catalyzed aerobic oxidative decarboxylation of amino acids

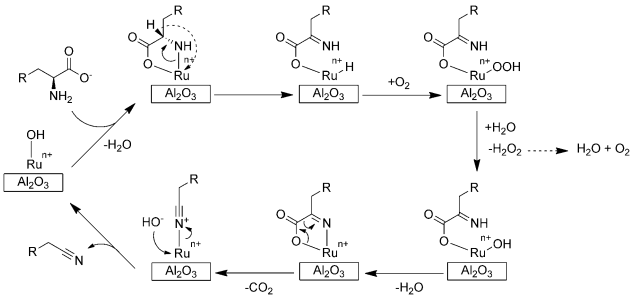


2a-8a 2b-8b

Amino acid	Nitrile	X^a [%]	S^b [%]
 2a	 2b	99	75
 3a	 3b	>99	83
 4a	 4b	>99	81
 5a	 5b	89	79
 6a	 6b	80	85
 7a	 7b	18	89
 8a	 8b	51	88

[a] Amino acid conversion. [b] Nitrile selectivity.

A potential mechanism for the ruthenium-catalyzed aerobic oxidative decarboxylation is proposed in Scheme 1. The resting state of the catalyst, a supported monomeric $Ru^{n+}(OH)$ species,[19] is the same as the one demonstrated to be involved in the aerobic alcohol and amine dehydrogenation.[12h,16] The α-amino acid enters the catalytic cycle by ligand exchange of the amino group on the Ru; the carboxylate might even displace another ligand in the Ru coordination sphere. Then, the Ru-amide species[20] undergoes β-hydride elimination into an α-iminocarboxylate and a Ru-monohydride species. The active $Ru^{n+}(OH)$ catalyst is regenerated *via* a hydroperoxide intermediate that is most probably formed by insertion of O_2 into the Ru-hydride bond.[19] Under the reaction conditions, the hydroperoxide or even H_2O_2 is rapidly decomposed by ruthenium. In a second stage, the Ru-coordinated α-iminocarboxylate is decarboxylated, with release of CO_2; and the catalyst is regenerated



Scheme 1 Proposed mechanism for the Ru-catalyzed oxidative decarboxylation of α-amino acids in the presence of molecular oxygen.

by replacement of the nitrile product by an incoming OH^- or fresh reactant.

In conclusion, alumina-supported hydrous ruthenium oxide is an efficient catalyst for oxidative decarboxylation of amino acids into nitriles and amides using molecular oxygen. Several aliphatic and functionalized amino acids are transformed successfully in water under mild conditions without producing halide waste.

LC, JV and IS are grateful to IWT Flanders and FWO Flanders for PhD fellowships. BL thanks KU Leuven (IOF-ZKC6712). DEDV acknowledges BELSPO (IAP-PAI P7/05) and the Flemish government (Methusalem grant CASAS) for structural funding. We thank Karel Duerinckx for assistance with NMR measurements.

Notes and references

1 P. Pollak, G. Romeder, F. Hagedorn and H.-P. Gelbeke, Nitriles, *Ullmann's Encyclopaedia of Industrial Chemistry*, Wiley-VCH, Weinheim, Germany, 2012.
2 T. M. Lammens, M. C. R. Franssen, E. L. Scott and J. P. M. Sanders, *Biomass Bioenergy*, 2012, **44**, 168.
3 L. Claes, R. Matthessen, I. Rombouts, T. De Baerdemaeker, D. Depla, J. A. Delcour, B. Lagrain and D. E. De Vos, *ChemSusChem*, 2015, **8**, 345.
4 J. Le Nôtre, E. L. Scott, M. C. R. Franssen and J. P. M. Sanders, *Green Chem.*, 2011, **13**, 807.
5 J.-J. Dai, Y.-B. Huang, C. Fang, Q.-X. Guo and Y. Fu, *ChemSusChem*, 2012, **5**, 617.
6 T. M. Lammens, J. Le Nôtre, M. C. R. Franssen, E. L. Scott and J. P. M. Sanders, *ChemSusChem*, 2011, **4**, 785.
7 (*a*) H. D. Dakin, *Biochem. J.*, 1916, **10**, 319; (*b*) H. D. Dakin, *Biochem. J.*, 1917, **11**, 79; (*c*) G. W. Stevenson and J. M. Luck, *J. Biol. Chem.*, 1961, **236**, 715; (*d*) G. Laval and B. T. Golding, *Synlett*, 2003, 542; (*e*) L. De Luca and G. Giacomelli, *Synlett*, 2004, 2180.
8 R. Matthessen, L. Claes, J. Fransaer, K. Binnemans and D. E. De Vos, *Eur. J. Org. Chem.*, 2014, 6649.
9 A. But, J. Le Nôtre, E. L. Scott, R. Wever and J. P. M. Sanders, *ChemSusChem*, 2012, **5**, 1199.
10 For homogeneously copper-catalyzed aerobic oxidations, see: (*a*) P. Capdevielle, A. Lavigne, D. Sparfel, J. Baranne-Lafont, N. K. Cuong and M. Maumy, *Tetrahedron Lett.*, 1990, **31**, 3305; (*b*) J. Kim and S. S. Stahl, *ACS Catal.*, 2013, **3**, 1652; (*c*) J. Wang, S. Lu, X. Cao and H. Gu, *Chem. Commun.*, 2014, **50**, 5637.
11 For homogeneous ruthenium-catalyzed aerobic oxidations, see: (*a*) R. Tang, S. E. Diamond, N. Neary and F. Mares, *J. Chem. Soc., Chem. Commun.*, 1978, 562; (*b*) A. J. Bailey and B. R. James, *Chem. Commun.*, 1996, 2343; (*c*) A. Taketoshi, T. Koizumi and T. Kanbara, *Tetrahedron Lett.*, 2010, **51**, 6457; (*d*) S. Aiki, A. Taketoshi, J. Kuwabara, T. Koizumi and T. Kanbara, *J. Organomet. Chem.*, 2011, **696**, 1301; (*e*) L. Cristian, S. Nica, O. D. Pavel, C. Mihailciuc, V. Almasan, S. M. Coman, C. Hardacre and V. I. Parvulescu, *Catal. Sci. Technol.*, 2013, **3**, 2646.
12 For heterogeneous ruthenium-catalyzed aerobic oxidations, see: (*a*) K. Mori, K. Yamaguchi, T. Mizugaki, K. Ebitani and K. Kaneda,

Chem. Commun., 2001, 461; (*b*) K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2003, **42**, 1480; (*c*) K. Yamaguchi and N. Mizuno, *Chem. – Eur. J.*, 2003, **9**, 4353; (*d*) E. C. Corker, U. V. Mentzel, J. Mielby, A. Riisager and R. Fehrmann, *Green Chem.*, 2013, **15**, 928; (*e*) Y. Zhang, K. Xu, X. Chen, T. Hu, Y. Yu, J. Zhang and J. Huang, *Catal. Commun.*, 2010, **11**, 951; (*f*) M. Kotani, T. Koike, K. Yamaguchi and N. Mizuno, *Green Chem.*, 2006, **8**, 735; (*g*) F. Li, J. Chen, Q. Zhang and Y. Wang, *Green Chem.*, 2008, **10**, 553; (*h*) K. Yamaguchi and N. Mizuno, *Synlett*, 2010, 2365; (*i*) M. T. Schümperli, C. Hammond and I. Hermans, *ACS Catal.*, 2012, **2**, 1108; (*j*) S. Venkatesan, A. S. Kumar, J.-F. Lee, T.-S. Chan and J.-M. Zen, *Chem. – Eur. J.*, 2012, **18**, 6147.

13 For other metal-catalyzed aerobic oxidations, see: (*a*) J. Gong, T. Yan and C. B. Mullins, *Chem. Commun.*, 2009, 761; (*b*) R. V. Jagadeesh, H. Junge and M. Beller, *ChemSusChem*, 2015, **8**, 92.

14 For ruthenium-catalyzed nitrile hydration, see: (*a*) K. Yamaguchi, M. Matsushita and N. Mizuno, *Angew. Chem., Int. Ed.*, 2004, **43**, 1576; (*b*) J. W. Kim, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2008, **47**, 9249; (*c*) V. Polshettiwar and R. S. Varma, *Chem. – Eur. J.*, 2009, **15**, 1582; (*d*) R. B. N. Baig and R. S. Varma, *Chem. Commun.*, 2012, **48**, 6220; (*e*) R. B. N. Baig, M. N. Nadagouda and R. S. Varma, *Green Chem.*, 2014, **16**, 2122.

15 Y. Wang, H. Kobayashi, K. Yamaguchi and N. Mizuno, *Chem. Commun.*, 2012, **48**, 2642.

16 (*a*) K. Yamaguchi, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *J. Am. Chem. Soc.*, 2000, **122**, 7144; (*b*) K. Yamaguchi, T. Koike, J. W. Kim, Y. Ogasawara and N. Mizuno, *Chem. – Eur. J.*, 2008, **14**, 11480.

17 K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2002, **41**, 4538.

18 S. Wuyts, D. E. De Vos, F. Verpoort, D. Depla, R. De Gryse and P. A. Jacobs, *J. Catal.*, 2003, **219**, 417.

19 F. Nikaidou, H. Ushiyama, K. Yamaguchi, K. Yamashita and N. Mizuno, *J. Phys. Chem. C*, 2010, **114**, 10873.

20 S. E. Diamond and F. Mares, *J. Organomet. Chem.*, 1977, **142**, C55.